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OXYGENATED FATTY ACIDS

Daniel Swern

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OXYGENATED FATTY ACIDS

Daniel Swern

I. INTRODUCTION

ALTHOUGH non-oxygenated fatty acids have been known and characterized since the early part of the nineteenth century, oxygenated fatty acids, with perhaps one notable exception (ricinoleic acid), were first characterized at the end of the nineteenth century, and they have been studied extensively and systematically only during the past twenty-five years. Oxygenated fatty acids have not yet achieved the industrial importance of non-oxygenated fatty acids, mainly because of their relative unavailability either from natural sources or synthetically. But interest in oxygenated fatty acids and applications for them continue to increase rapidly as more of their useful properties become better known and more efficient and inexpensive synthetic methods are developed for their preparation.

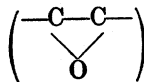
Oxygenated fatty acids are essential intermediates in a variety of basic studies in fatty acid chemistry, notably autoxidation, chemical oxidation, and reaction mechanism and metabolism investigations, and they are important in industrial processes concerned with the oxidation and drying of oils. Oxygenated fatty acids are also attractive substances for studies of position, geometrical and optical isomerism, and for studies of the effect of position, type and number of functional groups on physical and chemical properties. Most oxygenated fatty acids are higher melting and easier to crystallize than their corresponding non-oxygenated or unsaturated analogues, thus rendering them relatively easy to isolate and study. The opportunities which exist for isomerism, however, require that extreme care be taken in their preparation and isolation and in selecting criteria of purity.

In this chapter, both naturally occurring and synthetically prepared oxygenated fatty acids will be discussed. The emphasis, naturally, will be on those compounds containing eighteen carbon atoms since these exceed in importance by far all other oxygenated fatty acids combined. The classes of oxygenated fatty acids to be considered are epoxy acids, hydroxy acids and keto acids. The discussion will include their occurrence and isolation from natural sources or methods of preparation, physical and chemical characteristics, commercial utility, if any, and application to isomerism and structure studies.

II. EPOXY ACIDS

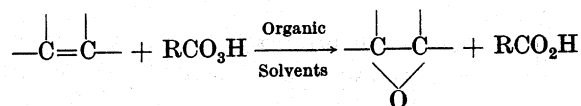
(a) Preparation

Epoxy fatty acids are straight-chain aliphatic monocarboxylic acids containing one or more oxirane groups



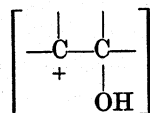
the fatty acid chain. This class of compounds does not occur in nature. Occasionally the isolation of epoxy acids from fats is reported, but in all probability the fat was not fresh and had undergone autoxidative changes.

The most important and most widely used method for the preparation of epoxy fatty acids is epoxidation of the corresponding olefinic acid with organic peracids, notably perbenzoic, peracetic and monopero-phthalic acids:^{(1), (2)}

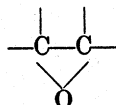


In some cases performic acid can be used. The reaction is rapid at or below room temperature, it proceeds in a homogeneous system, the product is easy to isolate and, in general, yields are good, frequently exceeding 80 per cent.

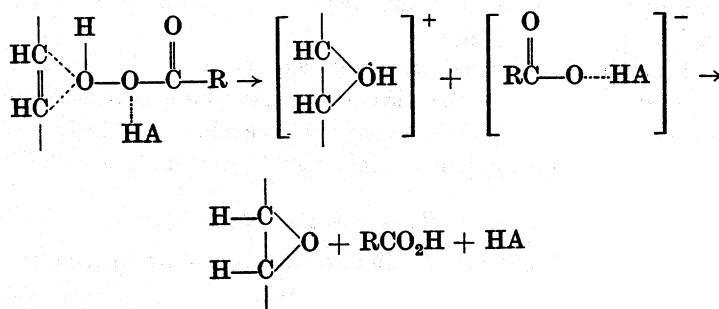
The epoxidation reaction is strikingly stereospecific, that is, the geometrical configuration of the resulting epoxy acid is identical with that of the olefinic acid from which it is derived. This high degree of stereospecificity precludes a free carbonium ion intermediate involving attack of the double bond by the simple electropositively polarized (electrophilic) hydroxyl group³ $[\ddot{O}:H]^+$ to yield



which on loss of a proton and ring closure yields

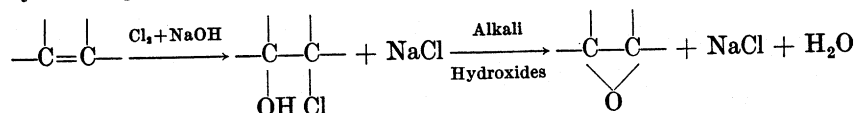


Since epoxidation is subject to general acid (HA) catalysis,^{(4), (5)} a more reasonable mechanism for the reaction would involve essentially direct formation of the conjugate acid of the oxirane by donation of $[\ddot{O}:H]^+$ to the double bond by a peracid-general acid complex:⁽¹⁾



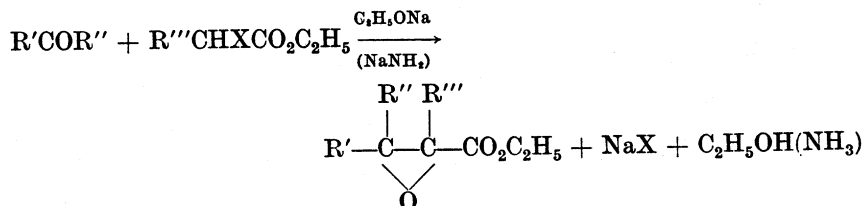
The olefin $-\ddot{\text{O}}:\text{H}]^+$ part of the transition state in such a process is similar to the so-called π -complexes.⁽⁶⁾ An attractive feature of this mechanism over that involving free $[\ddot{\text{O}}:\text{H}]^+$ is that it obviates any necessity for postulating rapid and reversible $[\ddot{\text{O}}:\text{H}]^+$ formation from peracid and general acid (HA) followed by slow attack of $[\ddot{\text{O}}:\text{H}]^+$ on the double bond. It is also a more reasonable path in the non-polar solvents often used as epoxidation reaction media.

The earliest method for the preparation of epoxy acids, and one which is still used to some extent, is hypochlorination of the olefinic acid followed by dehydrohalogenation:^{(7), (8), (9)}



The chlorohydrins can be prepared in substantially quantitative yield,⁽¹⁰⁾ but in large-scale experiments the dehydrohalogenation to the oxirane usually proceeds with difficulty and side reactions occur so that the overall yield of epoxy acids rarely exceeds 50 per cent. In small-scale experiments, however, excellent yields of epoxide can be obtained.⁽¹¹⁾

α,β -Epoxy esters can be prepared in fair to good yields by the Darzens condensation,⁽¹²⁾ which involves the reaction of an aldehyde or ketone with an α -halo ester in the presence of alkaline condensing agents, particularly sodium ethoxide or sodium amide:



This reaction has been explored to only a limited extent with aliphatic aldehydes and ketones containing more than five carbon atoms or with α -halo esters of high molecular weight acids.

Autoxidation of olefinic acids gives small yields of epoxy acids generally not exceeding 15 per cent. The difficulty in isolating the products, however, renders this method of little value.

Although many epoxy acids and esters have been prepared, the two most important members of this class and those which have been characterized the best are *cis*- and *trans*-9,10-epoxystearic acids, m.p. 59.5° and 55.5°, respectively, prepared from oleic or elaidic acid by epoxidation.^{(1), (2)}

(b) Properties and reactions

Epoxy acids are white crystalline solids which have melting points appreciably higher than those of the parent unsaturated acids. They are generally quite

soluble in the common organic solvents at or above room temperature, and are conveniently recrystallized from acetone, methanol or hexane. In general, epoxy acids show the typical reactions of ethylene oxide, that is, they react with many classes of compounds containing active hydrogen atoms, such as alcohols, amines, and acids. In the reaction of epoxy acids with alcohols in the presence of acid catalysts, the carboxyl group is esterified simultaneously with the ring-opening reaction to yield a hydroxy-ether-ester.⁽¹³⁾ Also, since mono-epoxy acids are bifunctional, those with the oxirane group in suitable positions can be readily converted to high molecular weight polyesters on heating.⁽¹⁴⁾ Hydrogenation, either catalytically^{(15), (16)} or with lithium aluminium hydride,⁽¹⁷⁾ converts the oxirane to the hydroxyl group. In the former reaction with 9,10-epoxystearic acid, it is believed that the resulting mixture of mono-hydroxy acids contains the 10-isomer to the extent of at least 85 per cent.⁽¹⁵⁾ Alkaline or acidic hydrolysis of epoxy acids converts the oxirane group to the α -glycol group with inversion.^{(18), (19)} Reaction of epoxy acids with carboxylic acids opens the oxirane ring and yields hydroxy-esters or diesters which can be thermally dehydrated and deacylated to conjugated dienes.⁽²⁰⁾ Reaction of epoxy acids with ammonia or amines yields long-chain amino acids also containing a hydroxyl group.⁽²¹⁾

Epoxy acids exhibit an interesting type of mixed stereoisomerism, existing both as optical as well as geometrical isomers. Thus, 9,10-epoxystearic acid contains two asymmetric carbon atoms, thereby furnishing two racemic mixtures, the high-melting (59.5°) and low-melting (55.5°) forms. In addition, because of the inability to undergo free rotation as a result of the oxirane group, these racemic mixtures are also geometrical (*cis*- and *trans*-) isomers. Recent x-ray diffraction studies have shown that the high-melting racemic mixture is *cis*- and the low-melting is *trans*-.⁽²²⁾

The infrared spectra of *cis* and *trans* epoxy fatty acids are substantially the same except that the *cis* isomer shows a characteristic absorption near 12 microns caused by the oxirane ring, whereas the *trans* isomer shows the characteristic absorption near 11.2 microns. Determination of infrared spectra and x-ray diffraction patterns, therefore, permit unequivocal identification of the *cis*- and *trans*-9,10-epoxystearic acids.⁽²³⁾ Furthermore, these physical measurements require only small samples and little time.

Industrial uses for the epoxy acids are limited. It has been shown recently that esters of epoxy acids are useful plasticizers and hydrogen chloride acceptors for use in polyvinyl chloride.⁽²⁴⁾ The neutralization of hydrochloric acid evolved when polyvinyl chloride is exposed to heat and/or light prevents the development of undesirable colour and rapid deterioration of the polymer. Epoxy esters are frequently referred to as stabilizing plasticizers for chlorine-containing polymers and they are used on a large industrial scale. The avidity with which epoxy fatty acids and their derivatives react with hydrogen chloride is the basis of an analytical method for their quantitative determination.⁽²⁵⁾ Epoxy acids are also cleaved by periodic acid, presumably because the oxirane is converted to the α -glycol by hydrolysis.

III. MONOHYDROXY ACIDS

The monohydroxy fatty acids are straight-chain aliphatic monocarboxylic acids containing one hydroxyl group in the aliphatic chain. They may be saturated or unsaturated. The naturally occurring hydroxy acids are optically active whereas the synthetic ones are inactive and are capable of being separated into optical isomers. The unsaturated hydroxy acids exhibit both optical and geometrical isomerism.

Generally speaking, saturated monohydroxy fatty acids do not occur to any significant extent as component acids of fats, waxes, and related materials. The waxy substances from leaves of certain coniferous plants, however, contain significant amounts of 12-hydroxydodecanoic (sabinic) acid and 16-hydroxyhexadecanoic (juniperic) acid.^{(26), (27)} Hydroxy fatty acids, such as 2-hydroxytetradecanoic and 2-hydroxyhexadecanoic acid, are present as components of wool wax.⁽²⁸⁾ Higher homologues are also assumed to be present. Brain lipids, notably the cerebrosides, contain 2-hydroxy acids of the C_{22} , C_{24} and C_{26} straight-chain series, with the C_{24} acid predominating.^{(29), (30), (31)} The presence of relatively large amounts of hydroxy fatty acids in brain lipids is a characteristic difference between the component fatty acids of brain lipids and the fatty acids present in animal fats. The biological function of the hydroxy acids in brain lipids is unknown and is of considerable fundamental and biochemical interest.

A monohydroxytetradecanoic acid has been isolated from the oil of *Angelica archangelica*.⁽³²⁾ Convolvulinolic acid, 11-hydroxypentadecanoic acid, has been isolated from the roots of plants of the *Convolvulaceae* family.⁽³³⁾ This acid is unusual since it contains an odd number of carbon atoms. An optically active monohydroxyhexadecanoic acid has been isolated from butter fat, but its structure has not been established.⁽³⁴⁾ Hydroxy fatty acids have also been isolated from the waxes of human and bovine tubercle bacilli,^{(35), (36), (37)} and leprosy bacilli.⁽³⁸⁾ High molecular weight fatty acids are reported to be present in the root fat of *Swertia japonica*,⁽³⁹⁾ in the hydrolysis products of cork^{(40), (41)} and in kidney lipids.⁽⁴²⁾

2-Hydroxy acids are important intermediates in biological oxidation of fatty acids and are also synthesized during insect and plant metabolism. Since the hydroxy acids are intermediates in many metabolic processes, they would not be expected to be present in large amounts.

(a) Preparation of saturated monohydroxy acids

The classical method for preparing monohydroxy fatty acids is hydrolysis of monohalogenated fatty acids with aqueous alkaline solutions.⁽³¹⁾ Halogenated fatty acids with the halogen originally in the 4- or 5- position readily form lactones on acidification of the soap solutions of the resulting hydroxy acids, especially if heated.

A convenient procedure for preparing monohydroxy compounds of known structure is hydrogenation or chemical reduction (with lithium aluminium hydride, for example) of the corresponding oxirane^{(15), (16), (17)} or keto compound.⁽⁴³⁾ No more than two isomers are apparently obtained from the oxirane

and recent evidence indicates that the isomer which predominates is the one in which the hydroxyl group is farther from the carboxyl group.⁽¹⁵⁾ As already discussed, the oxirane compounds can be conveniently prepared by epoxidation of olefinic acids with organic peracids. Keto acids of known structure can be prepared synthetically from shorter-chain intermediates by a variety of condensation reactions,⁽⁴³⁾ as will be discussed in a later section. By high pressure hydrogenation of the methyl esters of the corresponding keto acids, 3- through 17-monohydroxyoctadecanoic acids have recently been prepared.⁽⁴³⁾ The 2-isomer was prepared by alkaline hydrolysis of 2-bromooctadecanoic acid and the 18-isomer was prepared by hydrogenolyses of the monothiol ester of octadecane-1,18-dioic acid. The polymorphism of these, as well as the corresponding keto compounds, has been studied by thermal and x-ray methods.⁽⁴³⁾ It is now possible to identify unequivocally any isomeric monohydroxy or monoketo-octadecanoic acid or their methyl esters. The hydroxy compounds are more complicated with regard to polymorphic behaviour than the keto compounds.

Reaction of olefinic acids with concentrated sulphuric acid at low temperatures followed by hydrolysis of the intermediate sulphate esters also yields hydroxy acids, but complicated mixtures of isomers are obtained.^{(44), (45)}

Autoxidation of olefinic acids to α -hydroperoxides followed by complete hydrogenation has been reported for the preparation of saturated hydroxy acids.⁽⁴⁶⁾ Until good yields of specific hydroperoxides can be obtained by auto-oxidation, this procedure will be of only limited interest. Further, this procedure yields a mixture of isomeric hydroxy acids.⁽⁴⁶⁾ Partial reduction of α -hydroperoxido acids yields hydroxy unsaturated acids.⁽⁴⁶⁾

A newly discovered general reaction for the synthesis of monohydroxy acids, and one which appears to have wide applicability both on a laboratory and commercial scale, is the addition of 90 to 100 per cent formic acid at its boiling point to olefinic acids, followed by hydrolysis of the intermediate formate ester.⁽⁴⁷⁾ The reaction is markedly accelerated by strongly acidic catalysts, notably perchloric and sulphuric acids and boron fluoride. Yields of monohydroxystearic acids of over 70 per cent can be obtained. Two isomeric hydroxy acids predominate since, in the absence of directing influences, formic acid would be expected to add equally on each side of the double bond. Since the reaction involves carbonium ion intermediates, other isomeric hydroxy acids are also formed, but in small amounts. In some instances, the isomeric monohydroxy acids can be readily separated.⁽⁴⁷⁾ Acetic acid in the presence of acid catalysts also adds to the double bond but yields of monohydroxy acids are only about 40 per cent.⁽⁴⁷⁾ When a hydroxyl group is in close proximity to the double bond, as in the case of methyl ricinoleate and crotyl alcohol, formic acid addition does not take place. The failure to react in these cases may be explained on the assumption that the electron-withdrawing influence of the hydroxyl group lowers the electron density of the double bond below the point where attack by certain electrophilic (carbonium) ions is possible.

9-, 10-, 11-, 12- and 13-hydroxyoctadecanoic acids have been synthesized by the Grignard reaction from ω -aldehyde aliphatic acids and alkyl magnesium

Table 1. Saturated monohydroxy fatty acids^(a)

| Systematic name | M.P., °C | Methyl ester | |
|---|------------------------------------|----------------------------|-------------|
| | | M.P. | B.P., °C/mm |
| 2-Hydroxydodecanoic | 73-4° | 43° ^(b) | |
| 3-Hydroxydodecanoic | 70-70.5° | | |
| 4-Hydroxydodecanoic | 62.5-63.5° | | |
| 9-Hydroxydodecanoic | B.P. 156°/1 | | |
| 12-Hydroxydodecanoic | 84-85° | 34-35° | 164-166°/3 |
| 2-Methyl-2-hydroxyhendecanoic | 46° | | |
| 2-Hydroxytridecanoic | 78° | | |
| 4-Hydroxytridecanoic | 66-66.5° | | |
| 9-Hydroxytridecanoic | 49-51° | | 154-155°/3 |
| 13-Hydroxytridecanoic | 79-79.5° | 44° | |
| 2-Hydroxytetradecanoic | 81.5-82° | | |
| 3-Hydroxytetradecanoic | 72-73° | | |
| 11-Hydroxytetradecanoic | 51° | | |
| 14-Hydroxytetradecanoic | 91-91.5° | 47° | 196-198°/10 |
| 2-Hydroxypentadecanoic | 84.5° | 48° ^(b) | |
| 11-Hydroxypentadecanoic | 63.5-64° | 29-32° | 166°/2 |
| 15-Hydroxypentadecanoic | 84.5-85.2° | 52-52.5° | 180-182°/2 |
| 2-Hydroxyhexadecanoic | 86-87° | 59-60° | 230-231°/5 |
| 3-Hydroxyhexadecanoic | 83-83.5° | | |
| 11-Hydroxyhexadecanoic | 68-69° | 40.5-41.5° | 183-186°/3 |
| 16-Hydroxyhexadecanoic | 95° | 55-55.5° | 194-196°/2 |
| 2-Hydroxyheptadecanoic | 89° | | |
| 17-Hydroxyheptadecanoic | 87.5-88° | 58.6-59° | 210°/3 |
| 2-Methyl-16-hydroxyhexadecanoic | 62-63° | | |
| 2-Hydroxyoctadecanoic | 91° | 66°; 62-63° ^(b) | |
| 3-Hydroxyoctadecanoic | 89° | 51° | |
| 4-Hydroxyoctadecanoic | 87° | 56-59° | |
| 5-Hydroxyoctadecanoic | 82° | 52° | |
| 6-Hydroxyoctadecanoic | 83° | 58° | |
| 7-Hydroxyoctadecanoic | 78° | 51°; 37.5° ^(b) | |
| 8-Hydroxyoctadecanoic | 82° | 55.5° | |
| 9-Hydroxyoctadecanoic | 75° | 50.5°; 45-46° | 212-216°/4 |
| 10-Hydroxyoctadecanoic | 82° | 54° | 213-217°/4 |
| 11-Hydroxyoctadecanoic | 77° | 50° | 204-206°/4 |
| 12-Hydroxyoctadecanoic (optically active) | 82° | 58-59° | 202-204°/4 |
| 12-Hydroxyoctadecanoic (dl) | 79° | 53° | 185-189°/2 |
| 13-Hydroxyoctadecanoic | 77° | 53° | |
| 14-Hydroxyoctadecanoic | 77°(γ); 80°(ϵ) | 54.5° | |
| 15-Hydroxyoctadecanoic | 75.5° | 59° | |
| 16-Hydroxyoctadecanoic | 78.5° | 61° | |
| 17-Hydroxyoctadecanoic | 76.5°; 81° | 64° | |
| 18-Hydroxyoctadecanoic | 99° | 62.5° | |

Table 1—continued

| Systematic name | M.P., °C | Methyl ester | |
|--------------------------------|------------|-----------------------|-------------|
| | | M.P. | B.P., °C/mm |
| 2-Hydroxynonadecanoic . . . | 83–84° | | |
| 19-Hydroxynonadecanoic . . . | 91–91.5° | 65–5–66° | |
| 2-Hydroxyeicosanoic . . . | 91–92° | 62–64° | |
| 20-Hydroxyeicosanoic . . . | 97.4–97.8° | 68–68.5° | |
| 21-Hydroxyheneicosanoic . . . | 92.5–93° | 70–71° | |
| 2-Hydroxydocosanoic . . . | 98° | 70–71° ^(b) | |
| 13(14)-Hydroxydocosanoic . . . | 89–90° | 53° | |
| 2-Hydroxytetracosanoic . . . | 100° | | |
| 22-Hydroxytetracosanoic . . . | 95–96° | | |
| 2-Hydroxyhexacosanoic . . . | 86.5° | | |
| 2-Hydroxytriacontanoic . . . | 97.5° | | |
| 2-Hydroxytetracontanoic . . . | 109° | | |

^(a) The data in this table have been compiled mainly from BEILSTEIN's *Handbuch der Organischen Chemie*, Vol. III; DEUEL, H. J.; *Lipids*, Vol. I, Interscience Publishers, New York, 1951; DOSS, M. P.; *Properties of the Principal Fats, Fatty Oils, Waxes, Fatty Acids and Their Salts*, The Texas Co., New York, 1952; RALSTON, A. W.; *Fatty Acids and Their Derivatives*, John Wiley & Sons, New York, 1948; MARKLEY, K. S.; *Fatty Acids*, Interscience Publishers, New York, 1947; the literature references given in the section of this chapter entitled "Monohydroxy Fatty Acids," and unpublished research carried out in the author's laboratory.

^(b) Ethyl ester.

bromides. Thus, 9-hydroxystearic acid, m.p. 75°, can be prepared by condensing nonyl magnesium bromide with 9-aldehydononanoic acid followed by hydrolysis.⁽⁴⁸⁾

α -Hydroxy acids can be prepared by way of the intermediate cyanhydrins by reaction of aldehydes with hydrogen cyanide and a basic catalyst, followed by hydrolysis. The unavailability of long-chain aliphatic aldehydes severely limits the utility of this reaction in the fatty acid field. α -Hydroxy acids can also be prepared from aliphatic acids by reaction with bromine and red phosphorus, followed by hydrolysis.⁽⁴⁹⁾

β -Hydroxy acids can be readily prepared by the Reformatsky reaction.⁽⁵⁰⁾ This reaction involves the condensation of an aldehyde or ketone with an α -haloester in the presence of zinc. β -Hydroxyvaleric to β -hydroxystearic acid have been prepared in this way.^{(51), (52), (53), (54)}

ω -Hydroxy acids of the formula $\text{HO}(\text{CH}_2)_n\text{CO}_2\text{H}$ (where n is 7–20) have been prepared by CHUIT and co-workers^{(55), (56)} by a variety of methods, most important of which are the reduction of monoesters of dibasic acids with sodium and alcohol, and the reaction of potassium cyanide or sodium malonic ester with the monobromohydrins of α,ω -glycols and subsequent hydrolysis to the hydroxy acids.

Other reactions have been reported for the preparation of specific monohydroxy fatty acids, but the ones described are the most important by far.

Table I lists the better known saturated hydroxy fatty acids containing twelve or more carbon atoms.

(b) *Reactions and properties of saturated monohydroxy acids*

The presence of the hydroxyl group enhances the water and alcohol solubility of hydroxy acids and greatly reduces solubility in hydrocarbons. Hydroxy acids can usually be cleanly separated from unsaturated and saturated acids by a single crystallization from hexane. Final purification is readily effected by recrystallization from alcohols, acetone or other polar solvents. Mixtures of monohydroxy acids are usually difficult to separate into pure components because of similarity in properties.

Hydroxy fatty acids show typical alcoholic and carboxylic reactivity. The bifunctional character of the molecule makes some of them interesting in thermal polycondensation reactions. 2-Hydroxy acids, however, yield aldehydes, water, carbon monoxide and/or lactides when heated. 3-Hydroxy acids dehydrate readily to mixtures of unsaturated acids, and 4- and 5-hydroxy acids readily form lactones. Hydroxy acids in which the hydroxyl is farther from the carboxyl group polymerize readily on heating to yield polymeric esters, or dehydrate to unsaturated acids when heated to higher temperatures. Intermolecular esters of hydroxy acids are commonly referred to as estolides.

Numerous esters of monohydroxy fatty acids have been prepared. These have been suggested for use as high-melting waxes and release agents for plastics, and as intermediates in the preparation of plasticizers and surface-active agents.^{(57), (58), (59), (60), (61)} It has recently been reported that saturated monohydroxy acids are converted in fair yield to dicarboxylic acids on fusion with strong alkalis at 280 to 320°.⁽⁶¹⁾ The lithium salt of 12-hydroxystearic acid is an important ingredient in the preparation of high-quality, all-purpose, lubricating greases.

(c) *Unsaturated monohydroxy acids*

Ricinoleic acid, 12-hydroxy-*cis*-9-octadecenoic acid, apparently isolated for the first time by SAALMÜLLER in 1848,⁽⁶²⁾ is the most important unsaturated hydroxy acid. It occurs as a glycerol ester in oils of the species *Ricinus*, and in castor oil (oil from the seed of *Ricinus communis*) it forms over 85 per cent of the component glycerides.⁽⁶³⁾ It has also been reported in ivory wood oil (47 per cent), oil of ergot, argemone oil, and others. Other hydroxy unsaturated acids, some isomeric with ricinoleic acid, have also been reported in grapeseed oil, quinceseed oil, the oil from *Strophanthus sarmentosus*⁽⁶⁴⁾ and brain lipids. The unsaturated hydroxy acid in brain lipids is reported to be 2-hydroxy-9-tetracosenoic acid.⁽⁶⁵⁾ A highly unsaturated monohydroxy fatty acid (C₁₈H₂₆O₃) has recently been isolated from boleko (isano) oil.⁽⁶⁶⁾ Its structure has not been elucidated but the hydroxyl group is reported to be in the 8-position.

Pure ricinoleic acid has the following physical characteristics:⁽⁶⁷⁾ m.p. 5.0°

(γ), 7.7° (α), and 16.0° (β); n_D^{25} 1.4703; d_4^{25} 0.9417; $[\alpha]_D^{25} + 7.79^\circ$. Ricinoleic acid cannot be distilled satisfactorily because it readily undergoes dehydration and interesterification. The isolation of pure ricinoleic acid is extremely difficult and was achieved only recently by HAWKE,⁽⁶⁸⁾ who employed a modification of a published⁽⁶⁹⁾ low temperature solvent crystallization procedure used earlier in obtaining a purity of 97 per cent. Methyl ricinoleate of high purity can be prepared more readily and simply than the acid,^{(69), (70)} but saponification of the ester to obtain the pure acid is unsatisfactory.

Castor oil is of considerable commercial importance since its component ricinoleic glycerides can be dehydrated readily to a mixture of conjugated and non-conjugated linoleic acid glycerides, useful in surface coating applications.⁽⁷¹⁾ Reaction with aqueous alkali at high temperatures and preferably under pressure converts castor oil or esters of ricinoleic acid, as well as the free acid, to sebacic acid, an important component of plastics, plasticizers, and synthetic lubricants.^{(72), (73)} 2-Octanol is also formed in this reaction. Pyrolysis of ricinoleic acid yields undecylenic acid and heptaldehyde. Ricinelaidic acid, the *trans* isomer, melting point, 52° and $[\alpha]_D^{20} + 6.67^\circ$ (ethanol), is readily prepared from ricinoleic acid by reaction with oxides of nitrogen. This isomer can also be prepared directly from castor oil by elaidinization and hydrolysis. Ricinelaidic acid does not occur naturally.

IV. DIHYDROXY ACIDS

Dihydroxy fatty acids contain two hydroxyl groups in the fatty acid chain. Only saturated dihydroxy acids will be discussed here and the emphasis will be on those containing eighteen carbon atoms. The hydroxyl groups may be on adjacent (contiguous) or non-adjacent carbon atoms. The former (α -glycol) type are more important by far because reactions for their preparation have been well developed.

Dihydroxy fatty acids are uncommon in nature. The most important one is the optically active form of high-melting 9,10-dihydroxystearic acid, melting point 141° , which has been isolated in small amounts from the mixed fatty acids of castor oil⁽⁷⁴⁾ and, presumably, also from lycopodium oil.⁽⁷⁵⁾ 3,11-Dihydroxy-tetradecanoic (purolic) acid has been reported as a component acid of the seed fats of the South African and Japanese morning glories.^{(76), (77)} A dihydroxy acid (lanoceric acid), $C_{30}H_{60}O_4$, has apparently been isolated from wool wax.^{(78), (79)}

(a) Preparation

Two general and widely used methods are available for the preparation of dihydroxy fatty compounds of the α -glycol type. These are epoxidation of the corresponding olefinic acid with organic peracids followed by hydrolysis,^{(1), (2)} and oxidation of the olefinic acid with dilute cold alkaline potassium permanganate.⁽⁶³⁾ Yields of dihydroxy acid are good and frequently exceed 90 per cent.

Since each dihydroxy acid (with the exception of those with a terminal hydroxyl) contains two asymmetric carbon atoms, there are four optical

isomers possible or two racemic mixtures. As a rule the dihydroxy acid obtained by peracid oxidation of the *cis* form of the olefinic acid is the low-melting racemic mixture, and that obtained by potassium permanganate oxidation the high-melting racemic mixture.^{(18), (19)} As discussed earlier, epoxidation with organic peracids proceeds by *cis*-addition, but hydrolysis to the dihydroxy acid involves an inversion. On the other hand, potassium permanganate reacts by *cis* or normal addition. It is possible, therefore, to prepare the same racemic mixture of dihydroxy acids from the *cis* or *trans* form of the olefinic acid by oxidizing one with organic peracids and the other with alkaline potassium permanganate.

In the low-melting racemic mixture (for example, 9,10-dihydroxystearic acid, melting point 95°, prepared from oleic acid by peracetic acid oxidation and hydrolysis, or from elaidic acid by hydroxylation with alkaline potassium permanganate) the hydroxyl groups are closer together in space than in the high-melting racemic mixture (9,10-dihydroxystearic acid, melting point 131° prepared from oleic acid by hydroxylation with alkaline potassium permanganate, or from elaidic acid by peracetic acid oxidation and hydrolysis). This was recently shown to be the case in an unambiguous manner on the basis of the ability of the low-melting racemic mixture to form a urea complex readily whereas the high-melting racemic mixture did not.⁽¹⁹⁾ This conclusion is in accord with chemical evidence, namely, the comparative rates of cleavage of the isomeric 9,10-dihydroxystearic acids with periodic acid and lead tetraacetate.^{(80), (81)}

Other useful procedures for preparing contiguously substituted dihydroxy fatty acids are addition of halogen or hypochlorous acid to the olefinic acid followed by hydrolysis with aqueous or alcoholic alkali or silver oxide,⁽⁷⁾ reaction of olefinic acids with silver iodobenzoate (Prévost's reaction) followed by hydrolysis,^{(82), (83), (84)} oxidation of olefinic acids with *tert*-butyl hydroperoxide or hydrogen peroxide in *tert*-butyl alcohol in the presence of metal oxides, such as osmium tetroxide, vanadium pentoxide and chromium trioxide, which are capable of forming inorganic peracids,^{(85), (86), (87)} and photochemical addition of hydrogen peroxide to the double bond.⁽⁸⁸⁾ The Prévost reaction proceeds by *trans* addition to the double bond, whereas the photochemical or metal-catalyzed addition of hydrogen peroxide or *tert*-butyl hydroperoxide proceeds by *cis* addition.

Fig. 1 correlates the stereochemical relationships involved in the conversion of oleic and elaidic acids to the 9,10-dihydroxystearic acids by way of the intermediate oxirane and chlorohydroxy compounds.⁽¹⁸⁾ This scheme is self-consistent and is in harmony with accepted theories of the Walden inversion and double bond addition reactions. According to this scheme, epoxidation of the unsaturated acids with organic peracids, or oxidation with alkaline potassium permanganate, takes place by *cis* addition, whereas reaction with hypochlorous acid proceeds by *trans* addition. Furthermore, opening (either in alkaline or acidic media) and reforming of the oxirane ring, as well as replacement of a hydroxyl group of 9,10-dihydroxystearic acid with halogen, are each

accompanied by an inversion. An inversion also occurs when halogen is replaced by hydroxyl in the 9,10 (10,9)-halohydroxystearic acids. This scheme is generally applicable to olefinic acids, esters and alcohols and is now accepted by majority of investigators in the field.⁽¹¹⁾

Dihydroxy fatty acids in which the hydroxyl groups are non-contiguous are not well known. Reaction of ricinoleic acid with sulphuric acid followed by hydrolysis yields a dihydroxystearic acid, but the position of the hydroxyl groups is not known.⁽⁸⁹⁾ Reaction of linoleic acid with sulphuric acid gives a low yield of a dihydroxystearic acid of unknown structure and some monohydroxyoleic acid (by addition of sulphuric acid to only one of the double bonds in linoleic acid), as well as oxygen-linked polymers.⁽⁴⁴⁾ Formic acid adds to linoleic acid and, after hydrolysis, gives a good yield of a mixture of approximately equal parts of dihydroxystearic acid and monohydroxyoleic acid.⁽⁴⁷⁾ The structure of these compounds has not yet been reported. Reaction of formaldehyde with monoolefinic acids (Prins' reaction) in the presence of sulphuric acid yields a complex mixture of products^{(90), (91)} from which it has been claimed that cyclic dihydroxy compounds can be isolated.⁽⁹⁰⁾ This conclusion has been questioned.⁽⁹¹⁾

(b) *Reactions and properties*

Dihydroxy fatty acids are white, high-melting crystalline solids. The longer-chain members are insoluble in water whereas the shorter chain ones are either slightly or completely soluble (less than ten carbon atoms). They are soluble in hot oxygenated organic solvents, such as ethanol and acetone, but insoluble in hydrocarbons.

Dihydroxy fatty acids show both hydroxyl and carboxyl reactivity. However, esters or ethers in which only one hydroxyl group is bound up are best prepared by the reaction of the corresponding oxirane with an acid or alcohol, respectively. Reaction of the second hydroxyl group is somewhat more difficult to accomplish because of steric hindrance and/or electronic effects.^{(92), (93)}

Thermal treatment of contiguously substituted dihydroxy acids yields a variety of products depending on reaction time, temperature and catalysts used. For example, 9,10-dihydroxystearic acid has been reported to yield epoxystearic acid,^{(94), (95)} estolides,⁽⁹⁶⁾ 10-ketostearic acid,^{(95), (97)} hydroxyolefinic acids⁽⁹⁵⁾ and diunsaturated acids.⁽⁹⁵⁾ In the most recent report,⁽⁹⁵⁾ 9,10-dihydroxystearic or its methyl ester has been shown to yield 43 to 47 per cent conjugated diunsaturated acids, 31 to 36 per cent non-conjugated diunsaturated acids, 5 to 11 per cent keto acids, 7 to 8 per cent epoxy acids and 4 to 7 per cent hydroxyolefinic acid when heated to 290° with 0.5 per cent of toluenesulphonic acid for 3 minutes at 200 mm. Thermal polymerization of dihydroxy fatty acids yields polyesters, with the elimination of water. Since the acid molecules are trifunctional, cross-linking and gelation occur readily. Esters of the dihydroxy acids are bifunctional, however, and may be employed for the preparation of linear polymers by reaction with dibasic acids.⁽⁹⁸⁾

Contiguously substituted dihydroxy acids undergo a complicated reaction

when heated with aqueous alkali at high temperatures.^{(99), (100), (101), (102)} Presumably, they first dehydrogenate to the diketo acid which then undergoes a Favorskii rearrangement.⁽¹⁰²⁾ Thus, 9,10-dihydroxystearic acid is reported to yield 2-octyl-2-hydroxydecanedioic acid, and 9,10-dihydroxybehenic acid yields 2-octyl-2-hydroxytetradecanedioic acid.⁽¹⁰⁰⁾ The presence of potassium chlorate in the fusion reaction causes the aliphatic chain to cleave yielding mono- and dibasic acids.⁽¹⁰³⁾

Contiguously substituted dihydroxy fatty acids are readily cleaved to aldehydes with lead tetraacetate,^{(80), (104)} periodic acid,⁽⁸¹⁾ sodium bismuthate in acid medium,⁽¹⁰⁵⁾ and manganese tri-⁽¹⁰⁶⁾ or tetraacetate.⁽¹⁰⁷⁾

The 9,10-dihydroxystearic acids are the best known members of this class of compounds. The 2,3-dihydroxystearic acids⁽¹⁰⁸⁾ and those with the hydroxyl groups in the 6,7 through the 12,13-position have recently been studied in some detail.^{(109), (110), (111)} Both the low-melting and the high-melting series of 6,7-through 12,13-dihydroxystearic acids (obtainable, respectively, from the *cis* and *trans* series of octadecenoic acids by performic acid oxidation) show alternation of properties. By melting point and interplanar spacings, these acids can be classified into four sub-groups, namely, the even (6,7-, 8,9-, etc.) and the odd (7,8-, 9,10-, etc.) low-melting and the even and odd high-melting isomers. Within each sub-group the individual members cannot be satisfactorily distinguished by melting points and interplanar spacings. They can be distinguished, however, by the relative intensities of the different orders of their long spacings. The composition of mixtures of low- (95°) and high-melting (131°) 9,10-dihydroxystearic acids can be determined to within ± 3 per cent from the relative intensity of a selected pair of diffraction lines obtained in the x-ray powder patterns of such mixtures.⁽²²⁾

Table 2 lists the better known contiguously substituted dihydroxyoctadecanoic acids.

Table 2. Contiguously substituted dihydroxyoctadecanoic acids

| Hydroxyl positions | Low-melting Racemic mixtures ^(a) M.P., °C | High-melting Racemic mixtures ^(b) M.P., °C |
|---------------------------|--|---|
| 2,3. ^(c) . . . | 123–124° | 106–107° |
| 6,7. | 119° | 124° |
| 7,8. | 95–96° | 132–133° |
| 8,9. | 96–97° | 118–119° |
| 9,10. | 95° | 130–131° |
| 10,11. | 98–99° | 120–121° |
| 11,12. | 95–96° | 129–130° |
| 12,13. | 98.5° | 119–120° |

^(a) Prepared from the *cis*-forms of the corresponding octadecenoic acids by oxidation with performic acid.

^(b) Prepared from the *trans*-forms of the corresponding octadecenoic acids by oxidation with performic acid.

^(c) The 2,3-dihydroxystearic acids appear to be the exceptions to the rule that the low-melting racemic mixture is obtained by peracid oxidation of the *cis*-form of the octadecenoic acid.

V. POLYHYDROXY ACIDS

Preparation

The best known hydroxy fatty acids containing more than two hydroxyl groups in the fatty acid chain are those prepared from ricinoleic, linoleic and linolenic acids, and contain, respectively, three, four and six hydroxyl groups per molecule.

Hydroxylation of ricinoleic and ricinelaidic acids with alkaline potassium permanganate and peracetic acid yields four diastereoisomeric 9,10,12-trihydroxystearic acids formed in two inter-related pairs, as expected from theoretical considerations.⁽¹¹²⁾ The α - and β -acids, melting point 112° and 138°, are obtained, respectively, from ricinoleic acid by hydroxylation with alkaline potassium permanganate and from ricinelaidic acid by reaction with peracetic acid followed by hydrolysis. The γ - and δ -acids, melting point 87° and 110°, are similarly prepared from ricinelaidic and ricinoleic acids by hydroxylation with alkaline potassium permanganate and peracetic acid respectively.

Hydroxylation of octadecadienoic acids yields tetrahydroxystearic acids containing four asymmetric carbon atoms. Therefore, eight racemic mixtures and sixteen optically active forms should exist. The eight racemic mixtures of 9,10,12,13-tetrahydroxystearic acid have been prepared;⁽¹¹³⁾ these are called *sativic acids*. The spatial arrangements of the hydroxyl groups in each diastereoisomer have been deduced.⁽¹¹³⁾

Hydroxylation of linoleic acid with alkaline potassium permanganate⁽¹¹⁴⁾ yields two racemic forms, melting points 174° and 164°. Two additional racemic forms, melting points, 146° and 126° or 122°, are obtained from linoleic acid by treatment with hypochlorous and hypobromous acid followed by hydrolysis,⁽¹¹⁵⁾ by epoxidation of linoleic acid with peracetic acid followed by hydrolysis,⁽⁸³⁾ or by hydroxylation of linolelaidic acid with alkaline potassium permanganate.⁽¹¹⁶⁾ A third pair, melting points, 164° and 126° is prepared by the oxidation of the *trans-cis* or *cis-trans* geometric isomers of linoleic acid with alkaline potassium permanganate.⁽¹¹⁶⁾ The fourth pair, melting points 164° and 141.5°, is prepared from 9,10-dihydroxy-*cis*-12-octadecenoic acid by hydroxylation with alkaline potassium permanganate.⁽¹¹³⁾ The tetrahydroxystearic acids are slightly soluble in boiling water.

Hydroxylation of octadecatrienoic acids yields hexahydroxystearic acid containing six asymmetric carbon atoms. Of the thirty-two possible racemic mixtures (sixty-four optically active forms), only two have been adequately characterized.⁽¹¹⁷⁾ These are *linusic* and *isolinusic* acids, melting point 203° and 173.5°, respectively, prepared in low yield by oxidation of linolenic acid with alkaline potassium permanganate. No information on the spatial arrangement of the hydroxyl groups in these acids has been reported, although it is possible to make certain deductions on the basis of *cis*-hydroxylation. The hexahydroxystearic acids are soluble in boiling water.

VI. KETO ACIDS

(a) Preparation

Keto fatty acids are straight-chain aliphatic monocarboxylic acids containing one or more carbonyl groups in the fatty acid chain. They may be saturated or unsaturated.

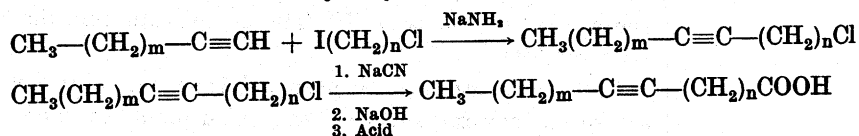
Only a few keto acids are naturally occurring. α -Licanic acid, 4-keto-9,11,13-octadecatrienoic acid, melting point 74° , is the major component acid (80 per cent) of the glycerides of oiticica oil. It was first described by WILBORN⁽¹¹⁸⁾ who isolated it from the seed fat of *Couepia grandiflora*, but its major source is oiticica oil obtained from the seed fat of *Licania rigida*.⁽¹¹⁹⁾ Mexican oiticica oil from *Licania arborea*⁽¹²⁰⁾ and po-yoak oil from *Parinarium sherbroense*⁽¹²¹⁾ are also good sources. Its structure was demonstrated by BROWN and FARMER⁽¹¹⁹⁾ who showed that its double bonds are conjugated and that it yields 4-keto-stearic acid on hydrogenation. Isomerization of α -licanic acid with iodine or sulphur, or exposure to sunlight, yields β -licanic acid,⁽¹¹⁹⁾ melting point, 97° .

Lactorinic acid, 6-ketostearic acid, melting point 86 to 87° , has been isolated in 1 to 3 per cent yield from the fat of the fungus *Lactarius rufus*,^{(122), (123)} and small amounts of keto acids are reported to be formed by the action of micro-organisms on fats.⁽³¹⁾

Most of the known keto acids are synthetic substances. The most frequently used synthetic methods are hydration of the corresponding acetylenic acids, condensation reactions involving β -keto esters (malonates or acetoacetates) and condensations using organo-metallic compounds (magnesium, zinc or cadmium).

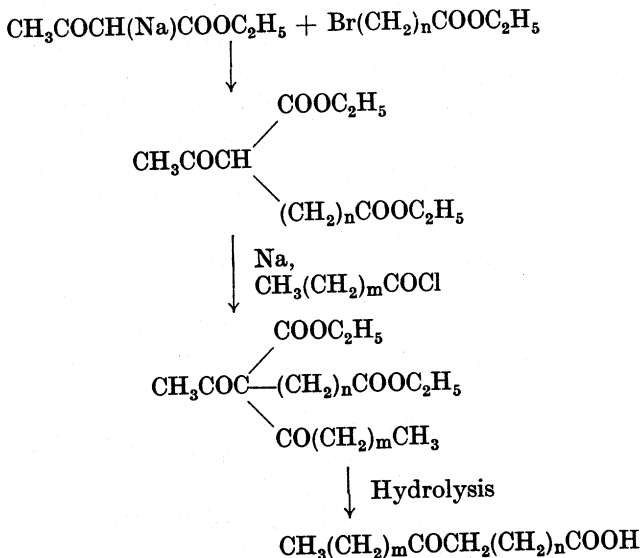
Hydration of the corresponding acetylenic acids in the presence of strong acids, such as formic and sulphuric, or by direct addition of water under pressure at high temperatures,^{(31), (124), (125)} are the classical methods for preparing keto fatty acids. Hydration of acetylenic acids has also been accomplished with alcoholic potassium hydroxide,⁽¹²⁶⁾ and by hydrolysis of the addition products of mercuric salts in acid media.⁽¹²⁷⁾ A mixture of two isomeric monoketo acids, which usually can be separated, is obtained by these reactions. Thus, hydration of stearolic acid, 9-octadecynoic acid, yields a mixture of 10-keto- and 9-ketostearic acid, the former predominating, and this ratio is reported to increase as the triple bond moves closer to the carboxyl group.⁽¹²⁵⁾

The development of methods for the synthesis of short-chain acetylenic compounds within the past decade, coupled with their commercial availability, has made the preparation of monoketo acids from acetylenic acids of considerably greater practical significance than formerly. Acetylenic acids can be readily prepared^{(109), (111), (126), (127), (127a), (127b), (128)} by condensing an alkyl-acetylene with an α,ω -chloroiodoalkane to yield a 1-chloroalkyne which is then converted to the nitrile and hydrolyzed to the alkynoic acid, as illustrated:



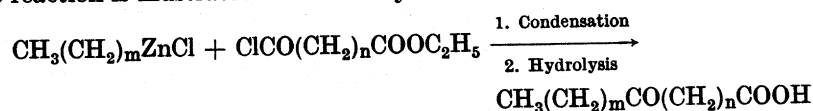
Another convenient method for preparing acetylenic acids, especially stearoli is from the corresponding olefinic acid by bromination and dehydrobromination with alcoholic potassium hydroxide⁽¹²⁹⁾ or, preferably, sodium amide in li ammonia.⁽¹³⁰⁾

Another important and widely used synthesis of monoketo acids is the condensation of carbethoxy acyl halides with the sodium derivative of either ethyl *n*-alkyl malonates or, preferably, ethyl 2-acetylalkanoates (alkyl acetoacetates) followed by cautious hydrolysis.^{(31), (131)} Yields of monoketo acids are fair, but improved yields can be obtained by condensing the sodium derivative of ethyl acetoacetate with ω -bromo esters and subsequent reaction with acyl chlorides followed by hydrolysis,⁽¹³²⁾ as illustrated—



Modifications and improvements of this synthetic procedure have been published.^{(43), (133), (134), (135)}

An excellent method for the preparation of keto acids is the condensation of alkyl magnesium halides, alkyl zinc halides, zinc dialkyls, or cadmium dialkyls with the acid chlorides of monoesters of dibasic acids.^{(31), (49), (136), (137), (138), (139)} The reaction is illustrated with an alkyl zinc halide:



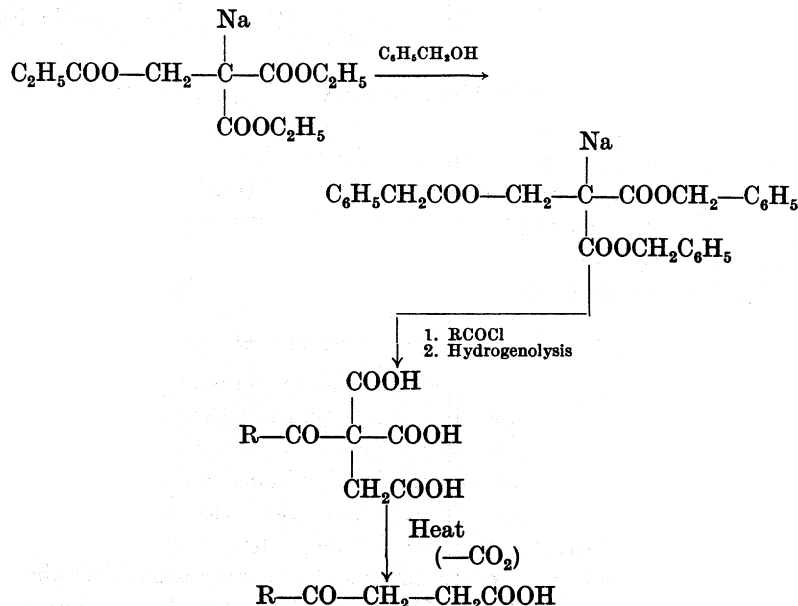
Excellent yields of keto acids containing up to 35 carbon atoms have been synthesized in this way.⁽¹³⁷⁾ The use of cadmium dialkyls has recently been reviewed.⁽¹³⁸⁾

Keto acids can also be prepared from the corresponding saturated or unsaturated hydroxy acids by controlled oxidation with chromic acid in acetic acid solution.^{(140), (141)} This reaction has recently been employed to prepare

contiguously substituted diketo acids from the corresponding dihydroxy acids.⁽¹¹¹⁾

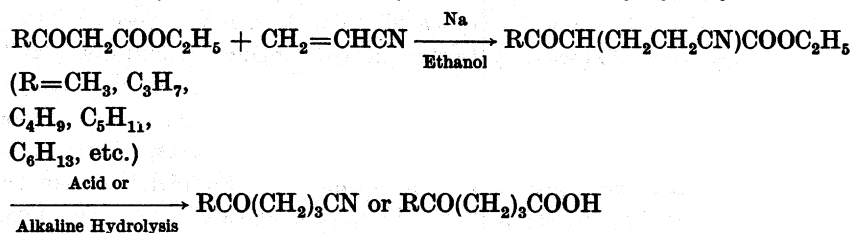
Synthetic methods which are specific for the synthesis of 2- and 3-keto acids are also known.^{(50), (51), (142), (143), (144)} Some of these are the Reformatsky reaction and hydrolysis of α -ketonitriles or α -oximino esters. The Reformatsky reaction is especially useful.

4-Keto acids can be prepared by a synthesis which takes advantage of the facile hydrogenolysis of benzyl esters.⁽¹⁴⁵⁾ In this sequence of reactions, illustrated below, the sodium derivative of triethyl ethane-1, 1,2-tricarboxylate is converted to its tribenzyl derivative which is then condensed with an acyl chloride. Catalytic debenzylation followed by decarboxylation yields the keto acid:



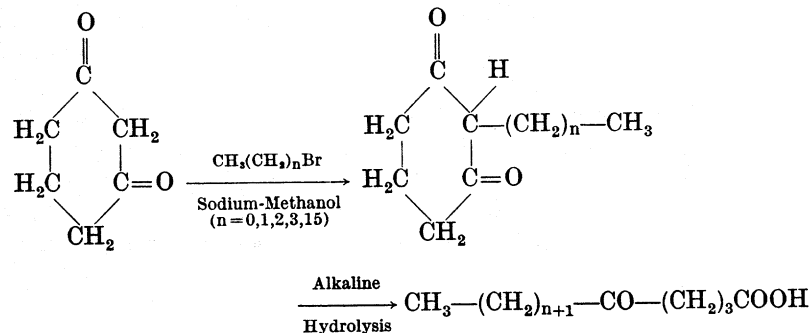
Other applications and modifications of this debenzylation synthesis have been published.^{(146), (147), (148), (149)}

In an interesting synthetic method recently reported, it was shown that C₆ through C₁₁ 5-keto aliphatic acids (or nitriles) can be prepared in fair yields by the reaction of β -ketoesters with acrylonitrile followed by hydrolysis:⁽¹⁵⁰⁾



The method appears applicable to longer-chain homologues.

Another interesting synthetic method for preparing 5-keto aliphatic acids in good yields involves C-alkylation of 1,3-cyclohexanedione, which exists predominantly as an enol, followed by alkaline hydrolysis:⁽¹⁵¹⁾



This procedure should be applicable to the preparation of the entire homologous series. It has also been used to prepare phenyl substituted and unsaturated keto acids, as well as dibasic acids.⁽¹⁵²⁾

Several of the synthetic methods described, or modifications of them, have recently been employed to prepare 2- through 17- keto-octadecanoic acids and their methyl esters.⁽⁴³⁾ As mentioned earlier, thermal and x-ray data have also been reported, thereby permitting unequivocal identification of any isomer.

(b) *Reactions and properties*

Keto fatty acids are white crystalline solids insoluble in water but soluble in hot organic solvents. They have typical ketone properties and form the usual derivatives with phenylhydrazine, hydroxylamine and semicarbazide. In general, keto acids are stable, distillable compounds but 2-keto acids lose carbon monoxide on heating and yield the next lower saturated acid.⁽¹⁵³⁾ Heating with aqueous sulphuric acid causes 2-keto acids to lose carbon dioxide yielding aldehydes containing one less carbon atom than the acids from which they are derived.⁽¹⁵⁴⁾ 3-Keto acids may also lose carbon dioxide readily to yield a ketone. Keto acids can be reduced to the corresponding hydroxy acids by catalytic hydrogenation or to saturated acids by the Clemmensen reduction.^{(31), (155)}

Monoketo fatty acids are useful in unequivocally proving the structure of monohydroxy and unsaturated acids. Hydroxy acids can be readily converted to the corresponding keto acids in high yields. These are then converted to the oxime followed by Beckmann rearrangement, hydrolysis and identification of the shorter-chain fragments.⁽¹⁵⁶⁾ The position of the double bond in oleic acid was first shown to be in the 9-position by conversion to stearolic acid and hydration to a mixture of 9- and 10-ketostearic acids, followed by the Beckmann rearrangement procedure just outlined.⁽¹⁵⁷⁾ Simpler techniques are now available for proving the position of double bonds and the keto acid-oxime procedure is infrequently employed.

Keto Acids

Table 3. Saturated monoketo fatty acids^(a)

| Systematic name | M.P., °C | Derivative |
|--|------------|--|
| 2-Ketododecanoic | 56.5-57° | Ethyl ester, b.p. 164-165°/13 Semicarbazone, m.p. 131° |
| 3-Ketododecanoic | | |
| 9-Ketododecanoic | 56° | |
| 10-Ketododecanoic | 72° | |
| 2-Ketotridecanoic | 62-62.5° | B.p., 185-186°/1 |
| 10-Ketotridecanoic | 63° | |
| 12-Ketotridecanoic | 70-71° | |
| 2-Ketotetradecanoic | 63-8° | |
| 3-Ketotetradecanoic | 39-40° | Semicarbazone, m.p. 253° Oxime, m.p. 74° |
| 4-Ketotetradecanoic | 87° | |
| 10-Ketotetradecanoic | 69° | Semicarbazone, m.p. 100° Ethyl ester, m.p. 28-29°; b.p. 164-166°/1 |
| 11-Ketotetradecanoic | 66-67° | |
| 13-Ketotetradecanoic | | |
| 12-Methyl-10-ketotridecanoic | 54-55° | |
| 12-Methyl-9-ketotridecanoic | 50.5-51° | Methyl ester, b.p. 181-183°/11 |
| 2-Methyl-12-ketotridecanoic | 46.5-47.2° | |
| 2-Ketopentadecanoic | 68-68.5° | |
| 4-Ketopentadecanoic | 92.6° | Methyl ester, m.p. 43.2-43.8°; b.p. 205-206°/15 |
| 11-Ketopentadecanoic | 70-71° | |
| 14-Ketopentadecanoic | 78.4-79.4° | |
| 2-Ketohexadecanoic | 69° | |
| 4-Ketohexadecanoic | 91-92° | Oxime, m.p. 54° |
| 5-Ketohexadecanoic | 88° | |
| 7-Ketohexadecanoic | 78° | |
| 8-Ketohexadecanoic | 77-78° | |
| 9-Ketohexadecanoic | 73.5-74.5° | |
| 10-Ketohexadecanoic | 75-75.8° | |
| 11-Ketohexadecanoic | 74-75° | |
| 14-Methyl-10-ketopentadecanoic | 68-69° | |
| 9-Ketoheptadecanoic | 78.5° | Semicarbazone, m.p. 111°; amide m.p. 119° |
| 2-Ketooctadecanoic | 74.5° | Methyl ester, m.p. 54° |
| 3-Ketooctadecanoic | 99° (dec.) | Semicarbazone, m.p. 295-300°; methyl ester, mp. 49° |
| 4-Ketooctadecanoic | 97° | Semicarbazone, m.p. 126°; oxime, m.p. 85°; methyl ester, m.p. 48° |
| 5-Ketooctadecanoic | 87°; 91° | Methyl ester, m.p. 54.5° |
| 6-Ketooctadecanoic | 87° | Oxime, m.p. 59-61°; methyl ester, m.p. 46.5° |
| 7-Ketooctadecanoic | 83° | Methyl ester, m.p. 49° |
| 8-Ketooctadecanoic | 84° | Methyl ester, m.p. 46.5° |
| 9-Ketooctadecanoic | 83° | Semicarbazone, m.p. 118-120°; methyl ester, m.p. 47.5° |
| 10-Ketooctadecanoic | 82.5° | Semicarbazone, m.p. 100-101°; methyl ester, m.p. 46°; ethylester, m.p. 41° |

Oxygenated Fatty Acids

Table 3—continued

| Systematic name | M.P., °C | Derivative |
|------------------------------------|--------------|---|
| 11-Ketooctadecanoic . . . | 82° | Methyl ester, m.p. 47° |
| 12-Ketooctadecanoic . . . | 81.5° | Semicarbazone, m.p. 125°; methyl ester, 45° |
| 13-Ketooctadecanoic . . . | 82° | Methyl ester, m.p. 47.5° |
| 14-Ketooctadecanoic . . . | 82° | Methyl ester, m.p. 49° |
| 15-Ketooctadecanoic . . . | 83° | Methyl ester, m.p. 53.5° |
| 16-Ketooctadecanoic . . . | 93° | Methyl ester, m.p. 54.5° |
| 17-Ketooctadecanoic . . . | 87.5° | Methyl ester, m.p. 56° |
| 16-Methyl-10-ketoheptadecanoic . . | 71.2–72° | |
| 10-Ketononadecanoic . . . | 86–87° | |
| 13-Ketoheneicosanoic . . . | 89–90° | Semicarbazone, m.p. 104–105° |
| 4-Ketodocosanoic . . . | 103° | |
| 10-Ketodocosanoic . . . | 94° | |
| 14-Ketodocosanoic . . . | 84.5° | Oxime, m.p. 49–51° |
| 10-Ketotricosanoic . . . | 93.5° | |
| 10-Ketotetracosanoic . . . | 94–94.5° | |
| 13-Ketotetracosanoic . . . | 95° | |
| 13-Ketotriacontanoic . . . | 104° | |
| 18-Ketononatriacontanoic . . . | 110.3–110.6° | |
| 13-Ketodotetracontanoic . . . | 110° | |

^(a) The data in this table have been compiled from the same reference works listed in footnote ^(a) of Table 1. The literature references given in the section of this chapter entitled "Keto Fatty Acids," and unpublished research carried out in the author's laboratory.

Alkyl esters of 12-ketostearic acid have been patented as plasticizers and stabilizers for gums and resins.⁽¹⁵⁸⁾

Table 3 lists the better known saturated monoketo fatty acids containing twelve or more carbon atoms.

VII. MISCELLANEOUS OXYGENATED FATTY ACIDS

(a) Hydroxyketo acids

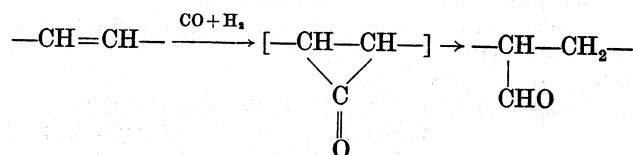
9 (10), 10 (9)-Hydroxyketostearic acids, apparently formed in equal amounts, have been prepared by oxidizing oleic and elaidic acids at low temperatures with neutral, dilute, aqueous potassium permanganate solution.^{(159), (160), (161)} Excess alkali must be avoided⁽¹⁶⁰⁾ otherwise an almost theoretical yield of high-melting, 9,10-dihydroxystearic acid, m.p. 131°, is obtained from oleic acid, and low-melting 9,10-dihydroxystearic acid, m.p. 95°, from elaidic acid.⁽¹⁶²⁾ The isomeric hydroxyketostearic acids have been separated by fractional crystallization of their semicarbazones, followed by hydrolysis.⁽¹⁶⁰⁾ 9-Hydroxy-10-ketostearic acid melts at 74°; 10-hydroxy-9-ketostearic acid

melts at 75.5°. Both isomers are readily soluble in most organic solvents. The mechanism of their formation from oleic acid is not known; 9,10-dihydroxyaric acid is not an intermediate.

The hydroxyketostearic acids are cleaved with periodic acid at room temperature and with acidic potassium permanganate at elevated temperatures.⁽¹⁶⁰⁾ Mild chromic acid oxidation yields diketostearic acid, and reduction yields 9,10-dihydroxystearic acid, melting point 131°. Fehling's solution and ammoniacal copper solutions are also reduced by hydroxyketostearic acids.⁽¹⁶⁰⁾ Of interest also is the facile cleavage of these acids in good yield in alkaline solution with gaseous oxygen to pelargonic and azelaic acids,^{(160), (161), (163)} The cleavage of the chain is dependent mainly on the excess of alkali present.⁽¹⁶¹⁾ In alkaline solution each of the hydroxyketostearic acids is converted to the equilibrium mixture in 24 to 36 hours at room temperature or within a few minutes at 100°. ⁽¹⁶⁰⁾

(b) Oxo reaction

Reaction of olefins under pressure with carbon monoxide and hydrogen in the presence of certain metallic catalysts yields aldehydes, as shown:



These are usually reduced further to the corresponding alcohols, or they can be oxidized to acids.^{(49), (164), (165)} If a long-chain olefin, such as methyl oleate, is the starting material one can prepare branched aldehydo acids, hydroxy acids or dibasic acids by means of this reaction. Although the oxo reaction has considerable promise, it has not received extensive study with long-chain olefinic materials derivable from fats.

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ADDENDUM (APRIL, 1954)

In the preparation of this chapter, the literature was consulted through 1952. Since then this field has been remarkably active and about fifty pertinent literature references have appeared. These are listed below in groups which correspond to the main subdivisions within the chapter.

Of interest are the papers by JUNGERMANN and SPOERRI and by MACK and BICKFORD who showed that the reaction of 9,10-epoxystearic acid with hydrogen chloride or hydrogen gave predominantly 10-hydroxy-9-chlorostearic acid and 10-hydroxystearic acid, respectively.

CHIBNALL, PIPER and WILLIAMS have shown conclusively that phrenosinic (cerebronic) acid is a mixture of 85 per cent α -hydroxytetracosanoic and 15 per cent α -hydroxyhexacosanoic acid. HORN, HUGEN and VON RUDLOFF have shown that α -hydroxy acids containing 12, 14, 16, and 18 carbon atoms comprise nearly 30 per cent of the acids of wool wax, with the C_{16} predominating. An unusual hydroxy acid, heptadec-10-en-8-yne-7-hydroxy-1-carboxylic acid, has been isolated by Ligthelm from the oil of *Ximenia caffra*.

By determination of the optical activity of the methyl esters and the acetyl derivatives of castor oil acids, BOLLEY has shown that castor oil contains 90-93 per cent of ricinoleic acid (as the glyceride). KNAFO has prepared pure ricinoleic acid from the mixed fatty acids of castor oil by acetylation of the hydroxy acids and precipitation of the straight-chain acids as urea complexes, followed by isolation of ricinoleic acid from the non-complexed acetates.

AEBI, VILKAS and LEDERER and ASSELINEAU have shown that α -mycolic acid is a mixture of a dihydroxy acid, $C_{87}H_{174}O_4 \pm 5CH_2$, with a hydroxy and methoxy acid. A provisional structure is reported for the dihydroxy acid. LOGAN has shown that 9,10-dihydroxystearic acid can be cleaved to azelaic and pelargonic acids in high yield by fusion with aqueous alkali at elevated temperatures. MCGHIE has prepared ketohydroxy acids from 9,10-dihydroxystearic and 13,14-dihydroxybehenic acids by oxidation with chromic acid to the corresponding diketo acids, followed by partial reduction with zinc.

Improved syntheses of ketones and keto acids have been described by BOWMAN and FORDHAM; BUU-HOI; KREUCHUNAS; LETTRÉ and JAHN; MANYIK FROSTECK, SANDERSON and HAUSER; SMUSZKOWICZ; STETTER and KLANI STETTER and DIERICHs; VISCONTINI; and YOHO and LEVINE.

GUNSTONE has reviewed recent developments in the preparation of natural and synthetic fatty acids.

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